REMARKS

Claims 20-33 and 42-54 are pending in the subject application. Applicants have hereinabove amended claims 20, 25, 31, 42, 47 and 52. Support for the amendments to the claims may be found in the specification, *inter alia*, as follows: claims 20 and 42 : page 9, lines 3-13; page 10 line 29 - page 11, lines 2; page 13, lines 16-22 and page 61, lines 3-5 and 25-28; table 2 on page 52, page 8, lines 23-24, page 35, lines 24-25 and page 51, lines 18-19; claims 25 and 47: page 10, lines 9 - 27; page 10 line 29 - page 11, line 8, page 8, lines 23-24, page 35, lines 24-25 and page 51, lines 18-19; page 61, lines 25-28; claims 31 and 52 : page 11, lines 17-22, page 13, lines 16-22; table 2, page 52, page 8, lines 23-24, page 35, lines 24-25 and page 51, lines 18-19, page 61, lines 25-28. Upon entry of this amendment, claims will 20-29, 31-33 and 42-54 will be pending and under examination.

Allowable Subject Matter

The Examiner indicated on page 2 of the August 21, 2010 Office Action that the indication of allowable subject matter set forth in the Advisory Action mailed August 13, 2009 is withdrawn. Specifically, the Examiner asserted that applicant's demonstration of unexpected results is not commensurate in scope of the claims. Specifically, the Examiner asserted that applicants have only demonstrated a synergistic effect when C6-ceramide is present in a much high amount than paclitaxel (e.g. a ration of 41.7:1 to 4,167:1). The Examiner indicated that favorable consideration would be given to claims which recite administration of C6-ceramide and paclitaxel in a ratio of 41.7:1 to 4167:1.

The Examiner further indicated that in view of the new rejections set forth in the August 21, 2009 Office Action the finality of the December 4, 2008 Office Action has been withdrawn and prosecution has been reopened.

Rejections Under 35 U.S.C. §103

1) Examiner's Rejections

In all of the remaining rejections under 35 U.S.C. §103 set forth in the August 21, 2009 Office Action, the Examiner asserted that the central issue remaining is whether or not the skilled artisan would have been motivated to administer a combination of paclitaxel and C6-ceramide to treat head and neck squamous carcinoma cells or pancreatic cancer cells.

a) Spencer et al. over Jayadev et al.

The Examiner rejected claims 20-29, 31-33 and 42-54 under 35 U.S.C. §103 as allegedly unpatentable over Spencer et al. (Drugs, 1994, vol. 48, pages 794-847) in view of Jayadev et al. (J. Bio. Chem., 1995, vol. 270, pages 2047 - 2052). The Examiner asserted that Spencer et al. disclose using paclitaxel as a chemotherapeutic agent for the treatment of cancers such as head and neck squamous cell carcinomas and pancreatic cancer, both alone as a single agent and in combination with other chemotherapeutic agents. The Examiner asserted that Jayadev et al. disclose that C_6-ceramide causes apoptosis in Molt-4 leukemia cells through significant G0/G1 arrest and that the effect of V6-ceramide on cell cycle arrest are a generalized phenomenon. Based on the foregoing, the Examiner concluded that it would have been prima facie obvious to one or ordinary skill in the art to administer paclitaxel in combination with C_6-ceramide as taught by Spencer et al. in view of Jayadev et al. The Examiner asserted that applicant's demonstrations of unexpected results are not commensurate in scope with claims. Specifically, the Examiner asserted that applicants have only demonstrated a synergistic effect when C_6-ceramide is present in a much higher amount than paclitaxel (e.g. a ration of 41.7:1 to 4167:1) and that applicants have not demonstrated whether such results occurs in ratios outside this range.

b) Spencer et al. over Cai et al.

The Examiner rejected claims 20-29, 31-33 and 42-54 under 35 U.S.C. §103 as allegedly unpatentable over Spencer et al. (Drugs, 1994, vol. 48, pages 794-847) in view of Cai et al. (J. Bio. Chem., 1997, vol.

272, pages 6918 - 6926). The Examiner asserted that Spencer et al. disclose using paclitaxel as a chemotherapeutic agent for the treatment of cancers such as head and neck squamous cell carcinomas and pancreatic cancer, both alone as a single agent and in combination with other chemotherapeutic agents. The Examiner asserted that Cai et al. discloses that C_6-ceramide induces apoptosis in both TNF-sensitive and TNF-resistant breast cancer cells.. Based on the foregoing, the Examiner concluded that it would have been prima facie obvious to one or ordinary skill in the art to administer paclitaxel in combination with C_6-ceramide as taught by Spencer et al. in view of Cai et al. The Examiner asserted that applicant's demonstrations of unexpected results are not commensurate in scope with claims. Specifically, the Examiner asserted that applicants have only demonstrated a synergistic effect when C_6-ceramide is present in a much higher amount than paclitaxel (e.g. a ration of 41.7:1 to 4167:1) and that applicants have not demonstrated whether such results occurs in ratios outside this range.

c) Spencer et al. in view of Wei et al.

The Examiner rejected claims 20-29, 31-33 and 42-54 under 35 U.S.C. §103 as allegedly unpatentable over Spencer et al. (Drugs, 1994, vol. 48, pages 794-847) in view of Wei et al. (U.S. Patent No. 5,631,394 issued May 20, 1997). The Examiner asserted that Spencer et al. disclose using paclitaxel as a chemotherapeutic agent for the treatment of cancers such as head and neck squamous cell carcinomas and pancreatic cancer, both alone as a single agent and in combination with other chemotherapeutic agents. The Examiner asserted that Wei et al. disclose that increases in ceramide concentrations can stimulate apoptosis and that C_6-ceramide inhibits growth of human and mouse cancer cell lines *in vitro*. Based on the foregoing, the Examiner concluded that it would have been prima facie obvious to one or ordinary skill in the art to administer paclitaxel in combination with C_6-ceramide as taught by Spencer et al. in view of Wei et al. The Examiner asserted that applicant's demonstrations of unexpected results are not commensurate in scope with claims. Specifically, the Examiner asserted that applicants have only demonstrated a synergistic effect

when C_6-ceramide is present in a much higher amount than paclitaxel (e.g. a ration of 41.7:1 to 4167:1) and that applicants have not demonstrated whether such results occurs in ratios outside this range.

2) Applicants' Response

In response, applicants respectfully traverse the Examiner's ground of rejection. Nevertheless, without conceding the correctness of the Examiner's rejection but in order to expedite prosecution, applicants note that claims 20, 25, 31, 42, 47 and 52 have been amended hereinabove.

As amended, claims 20, 25, 31, 42, 47 and 52 now recite, in relevant part, "and wherein the ratio of the amount of C_6-ceramide relative to the amount of paclitaxel is at least 4.167 to 1".

The specification discloses, *inter alia*, at page 61-62, that Tu138 (head and neck squamous carcinoma cells) were implanted subcutaneously in nude mice which were treated beginning at day 4 with thrice weekly injections of paclitaxel (120 µg in 0.1ml, alone, C_6-ceramide, 500 µg in 0.2ml, alone, or combinations thereof and control. This results in a ratio the amount of C_6-ceramide to the amount of paclitaxel of 4.167:1. As shown in Figures 11 and 12, tumor growth was significantly inhibited by combination of paclitaxel and ceramide. For example, in Figure 11, after five weeks of treatment, the average size of tumor was just over 50 $(mm)^2$ in the case of treatment with combination paclitaxel and C_6-ceramide. In contrast, the average size of tumor was just under 100 $(mm)^2$ for C_6-ceramide alone and just under 250 $(mm)^2$ for paclitaxel alone. In addition, the specification discloses that in human Tu138 head and neck squamous carcinoma cells lines, paclitaxel in combination with C_6-ceramide inhibited growth of the Tu138 cells by 66% as compared to growth inhibition of only 10% and 28% upon administration of each of paclitaxel and C_6-ceramide alone.

Accordingly, applicants have demonstrated *in vivo* an unexpected effect on growth inhibition of head and neck squamous carcinoma cells with the

combination of paclitaxel and C_6-ceramide wherein the ratio of the amount of C_6-ceramide to the amount of paclitaxel is at least 4.167 to 1.

The specification discloses on page 52, in Table 2, that in RWP-2 human pancreatic cell lines, the combination of 600 ng/ml paclitaxel and 25 µg/ml C_6-ceramide inhibited growth of the RWP-2 cells bys 75% as compared to growth inhibition of only 2% and 6% with administration of each of the agents alone, respectively. Moreover, as demonstrated in the 1.132 Declaration of Dr. Harold J. Wanebo submitted with applicants' previous response, applicants have demonstrated *in vivo* an unexpected effect on growth inhibition of pancreatic cancer cells with the combination of paclitaxel and C_6-ceramide.

Accordingly, applicants maintain amended claims 20, 25, 31, 42, 47 and 52 and the claims are commensurate in scope with the specification.

In view of the preceding remarks, applicants respectfully request that the Examiner reconsider and withdraw the grounds of rejection under 35 U.S.C. §103 set forth in the August 21, 2009 Office Action

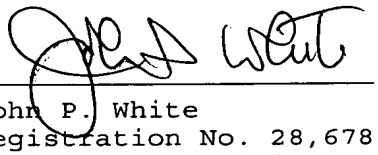
Conclusion

In view of the remarks hereinabove, applicants respectfully submit that the grounds of rejection set forth in the August 21, 2009 Office Action have been overcome. Applicants respectfully solicit a Notice of Allowance.

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorney invites the Examiner to telephone him at the number provided below.

No fee, other than the enclosed $555.00 fee for filing a three-month extension of time is deemed necessary in connection with the filing of this Amendment. However, if any additional fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 03-3125.

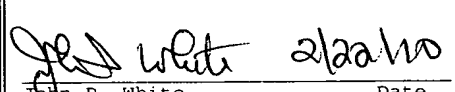
Respectfully submitted,



John P. White
Registration No. 28,678
Attorney for Applicants
Cooper & Dunham, LLP
30 Rockefeller Plaza, 20th Floor
New York, New York 10112
(212) 278-0400

I hereby certify that this correspondence is being deposited this date with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to:

Mail Stop Amendment
Commissioner for Patents,
P.O. Box 1450,
Alexandria, VA 22313-1450.



John P. White Date
Reg. No. 28,678